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OCCUPATIONAL HEALTH HAZARDS OF NITROGLYCERIN WITH SPECIAL EMPHASIS ON TOLERANCE AND WITHDRAWAL EFFECTS -- A LITERATURE REVIEW

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This literature review was conducted to update the information on nitroglycerin effects related to the development of tolerance and withdrawal in humans and experimental animal models. Also discussed are reports on the carcinogenicity of nitroglycerin. Data from industrial hygiene surveys at Army ammunition plants and recommendations for additional health-effects research on nitroglycerin are included.

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INTRODUCTION

The US Army Medical Bioengineering Research and Development Laboratory at Ft. Detrick, Frederick, Maryland conducts toxicologic research on chemicals which may produce adverse health effects in workers at Army activities. The ammunition plants and their related "load/assembly/pack" and "washout" facilities constitute one of the major Army industrial activities and these activities are a potential source of occupational exposures to toxic chemicals. The occurrence of adverse health effects resulting from exposures to one or more munitions compounds has been associated with these Army activities. Thus, research efforts are needed to define threshold exposure limits which insure worker health protection.

The hazard assessment strategy involves, as a first step, an extensive review of published and unpublished information; evaluation of information gathered; and identification of specific tasks required to fill the information gaps. Research projects are then specifically tailored to acquire the additional data-base necessary to complete the toxicologic profile of a given chemical or a mixture. The final step in this process is to submit the data-base to the appropriate regulatory agency as a basis for setting temporary guidelines which may later be accepted as standards.

This literature review concentrates on information concerning the development of tolerance to nitroglycerin, in occupational as well as in experimental settings, with emphasis on coronary vascular effects following withdrawal from long-term exposures to nitroglycerin. Pertinent information from publications in the open literature as well as industrial hygiene and occupational health surveys prepared by the US Army Environmental Hygiene Agency at Aberdeen Proving Ground, Maryland are herein summarized. The on-going studies on nitroglycerin supported by the US Army Medical Research & Development Command are also discussed. This review includes a list of recommendations for additional research to provide a data-base from which standards may be established.

EFFECTS ON HUMANS AND OTHER MAMMALS

Several literature reviews are available on the toxicologic, physiologic and pharmacologic effects of nitroglycerin. Von Oettingen (1946)[1] prepared a comprehensive summary of work published to that date. In later reports the acute toxicology of nitroglycerin was reviewed by Munch and Friedland (1965)[2] and the chronic toxicology of nitroglycerin was reviewed by Munch *et al.* (1965).[3] Nickerson (1970)[4] reviewed the literature on nitroglycerin effects including its pharmacologic effects on the cardiovascular system, as well as its absorption, excretion, toxicity, tolerance, and therapeutic uses in man. More recently, Cohn and Gorlin (1974)[5] reviewed the physiologic actions of nitroglycerin with special

emphasis on coronary circulatory effects. Dacre and Rosenblatt (1974)[6] summarized the published data on acute and chronic mammalian nitroglycerin toxicity. This report expanded the scope of information on nitroglycerin toxicity by including a consideration of the carcinogenic, mutagenic and teratogenic potentials of nitroglycerin. The most recent comprehensive treatise on the chemistry, metabolism and physiologic-pharmacologic effects of organic nitrates to include nitroglycerin has been edited by Needleman (1975).[7]

The pertinent publications dealing with health related effects of nitroglycerin published from 1973 to 1975 are listed in Table 1. In the human subjects, sublingual administrations varied from 0.3 mg to 0.6 mg of nitroglycerin. Assuming that the average weight of the test subjects was 70 kg, the dosage may have ranged from 0.005 - 0.01 mg/kg. Changes in myocardial enzymes, coenzymes, electrochemical aspects of cardiac function, and subjective symptoms such as headaches were reported. Dogs, rabbits, guinea pigs, rats, and cats were also used as experimental models with the dog being the most frequently used species. With the exception of two *in vitro* studies, nitroglycerin was administered intravenously. These studies are cited in this report to provide estimates of the range of dosages used in different species, and to estimate the effective dose in dogs. The latter information will be useful in potential studies conducted by this laboratory.

TOLERANCE TO NITROGLYCERIN

Induction of tolerance and cross-tolerance *in vivo* and *in vitro* has been discussed by Rush *et al.* (1971),[35] Johnson *et al.* (1973)[36] and Needleman and Johnson, Jr. (1973).[37] More recently, Needleman and Johnson, Jr. (1975)[7] have consolidated the information on organic nitrate induced tolerance in the cardiovascular responsiveness to these compounds. They cite evidence that tolerance to nitroglycerin is (1) a dose- and time-dependent phenomenon; (2) not the result of increased biotransformation or increased sympathetic compensatory responses. These authors have proposed a unifying hypothesis which suggests that tolerance occurs when organic nitrates react with reduced sulfhydryl groups in the vascular smooth muscle receptor leading to the formation of a disulfide linkage and the release of inorganic nitrite. Presumably this reaction converts the nitrate receptor to the disulfide form which has a lower affinity for organic nitrates. By determining the mechanism leading to organic nitrate tolerance, the mechanism(s) involved in the withdrawal effects may eventually be defined. The dose-response characteristics of the withdrawal effects have not been determined. Thus, functional impairment of coronary blood flow resulting in localized ischemia of cardiac tissue must be examined as a function of dose and time of nitroglycerin exposure to evaluate the withdrawal mechanisms.

TABLE 1. SUMMARY OF NITROGLYCERIN STUDIES WITH HUMAN SUBJECTS AND EXPERIMENTAL ANIMAL MODELS

Dose (Route)	Species	Reference
0.3 mg (sublingual)	Human	8
0.4 mg (sublingual)	Human	9
2% (cutaneous)	Human	10
0.4 mg (sublingual)	Human	11
0.6 mg (sublingual)	Human	12
0.4 mg (sublingual)	Human	13
0.5 mg (sublingual)	Human	14
0.00001 mg/kg (i.v.)	Dog	15
0.00002 mg/kg (i.v.)	Dog	16
0.00003 mg/kg (i.v.)	Dog	17
0.3 to 1.7 mg/min (i.v.)	Dog	18
0.000005 mg/ml (in vitro)	Rabbits	19
0.000005-0.00001 mg/min (i.v.)	Dog	20
0.000001-0.00001 mg/ml (in vitro)	Guinea pig	21
0.00002 mg/kg (i.v.)	Guinea pig	22
0.000015-0.0001 mg/kg (i.v.)	Guinea pig	23
1 mg/kg (i.v.)	Rat	24
0.05-0.2 mg/kg (i.v.)	Dog	25
0.000003 mg/kg/min (i.v.)	Dog	26
0.5 mg/kg (i.v.)	Dog	27
0.00001, 0.00002 & 0.00005 mg/kg (i.v.)	Dog	28
0.000003 mg/kg/min (i.v.)	Dog	29
0.00000515 mg/kg/min (i.v.)	Dog	30
0.00002 mg/kg (i.v.)	Dog	31
0.5 mg/kg (i.v.)	Dog	32
0.00002 mg/kg (i.v.)	Dog	33
3 mg/kg (i.v.)	Dog	34
18 mg/kg (i.v.)	Cat	34
2 mg/kg (i.v.)	Rat	34
750 mg/kg (intraportal vein)	Dog	34
300 mg/kg (intraportal vein)	Cat	34
190 mg/kg (intraportal vein)	Rat	34

The studies reporting experimental induction of nitrate tolerance *in vivo* are listed in Table 2. The specific endpoint used to test for the development of tolerance usually differed from study to study. The only common factor was that all of the criteria used were related to the acute cardiovascular response to nitrates. Furthermore, this table was restricted to *in vivo* studies on nitrate tolerance because of our specific interest in this information for anticipated research projects. Tolerance to nitrates develops in humans within a few days as reported by Crandall (1933),[38] Schelling and Lasagna, Jr. (1967),[39] and Zelis and Mason (1969).[41] Tolerance to nitrates has also been experimentally produced in dogs, rabbits, rats, and mice (see Table 2). A recent report by Lange *et al.* (1972)[53] suggests that circulating nitroglycerin and/or its metabolites initially produce sustained vasodilation. This acute effect is eventually compensated by homeostatic mechanisms such that the vessel diameters return to their pre-exposure sizes thus achieving a state of tolerance. The induction of a state of tolerance to the acute effect of nitroglycerin may result in cardiovascular consequences during withdrawal from chronic nitroglycerin exposures. Symptoms such as chest pains which resemble attacks of angina pectoris, coronary artery spasms and sudden deaths have been reported during this withdrawal phase [Schwartz (1946),[49] Carmichael *et al.* (1963),[50] Lund *et al.* (1968)[51] and Lanfranchi and Beraud (1969)].[52]

MUTAGENIC-TERATOGENIC-CARCINOGENIC POTENTIAL OF NITROGLYCERIN

For long-term sublethal exposures to nitroglycerin, the mutagenic, teratogenic and carcinogenic potential of nitroglycerin and/or its metabolic degradation products are of major clinical importance.

No information on teratogenic effects was found in the reviewed literature. However, with regard to testing nitroglycerin for any mutagenic (or carcinogenic) activity, Lee *et al.* (1976)[54] reported no mutagenic effects of nitroglycerin at concentrations which killed 65% and 99% of the cell population in an *in vitro* Chinese hamster ovary system. The carcinogenic potential of nitroglycerin was examined by two other groups. Takayama (1975)[55] reported that, feeding male and female rats a 3% nitroglycerin solution as drinking water for 10 months and observing for 8 additional months, the incidence of mammary tumor formation was not statistically different from that of the control group. Suzuki *et al.* (1975)[56] administered nitroglycerin to male and female mice in drinking water using solutions of 330, 40 and 10 mg/l of nitroglycerin. The highest dose was given for 12 months and the lower doses for 18 months. Both groups were studied for a total duration of 18 months. Again, it was concluded that nitroglycerin did not induce a statistically significant increase in the incidence of tumors over the control group.

TABLE 2. EXPERIMENTAL INDUCTION OF NITRATE TOLERANCE IN VIVO

Species	Organic[a] Nitrate	Treatment Protocol	Route of Administration	Reference
Human	NG, ETN, EGDN	Total amount required to develop headache tolerance NG=52.5 mg, ETN= 45 mg, EGDN=170 mg	Subcutaneous	38
Human	PETN	10 mg, 4 times daily for 2 weeks and 20 mg, 3 times daily for 2 weeks	Sublingual	39
Human	NG	0.3 mg, 17 times during 8 hr span for 3 days	Sublingual	40
Human	ISD	120 mg/day for 6 weeks	Sublingual	41
Dog	NG	1 mg/kg, 20 times a day for 4 days	Subcutaneous	42
Dog	NG	1 mg/kg for 1 hr	Continuous Intravenous Infusion	35
		1 mg/kg, 20 times a day	Subcutaneous	35
Rabbit	$NaNO_2$	30 mg/kg, 3 times daily for 7 days	Subcutaneous	43
Rabbit	NG	1 mg/kg every 30 min from 0800 to 2000 for 4 days	Subcutaneous	44
Rat	EGDN	20 mg/kg, 3 times daily for 5 days	Intramuscular	40
Rat	EGDN	65 mg/kg daily, 5 days/ week for 10 weeks	Subcutaneous	45
Rat	EGDN	65 mg/kg daily, 5 days/ week for 5 weeks	Subcutaneous	46
Rat	NG	10, 25 or 100 mg/kg, 3 times daily for 7 days	Subcutaneous	47
Rat	EGDN	65 mg/kg daily, 5 days/ week for 8 weeks	Subcutaneous	48
Rat	NG	100 mg/kg, 3 times daily for 3 or 4 days	Subcutaneous	36
Mouse	EGDN	75 mg/kg, 3 days at 12-hour intervals	Subcutaneous	36

a. Abbreviations:

NG = nitroglycerin
ETN = erythritol tetranitrate
PETN = pentaerythritol tetranitrate
ISD = isosorbide dinitrate
$NaNO_2$ = sodium nitrite
EGDN = ethylene glycol dinitrate

SCREENING TESTS FOR HYPERSUSCEPTIBILITY TO NITROGLYCERIN

Current occupational health standards do not assure equal protection for all workers. A small segment of any worker population commonly responds to exposures well below the limits set by standards, as discussed by Stokinger (1972).[57] Stokinger et al. (1968)[58] and Stokinger and Scheel (1973)[59] have expressed the need for the development of tests to screen for hypersusceptible employees. They also discussed the potential use of such tests in industry. These tests may identify those individuals predisposed to be hypersusceptible to certain chemicals and thus provide a means of reducing unnecessary health risks. With specific reference to possible nitroglycerin hypersusceptibility, Phipps (1972)[60] has reported that hyperthyroidism potentiates the acute toxicity to organic nitrates, whereas, hypothyroidism antagonizes the acute effects. A test for hyperthyroidism may reduce the health risk faced by certain individuals.

The development of such tests should consider the spontaneous circadian (~24 hours) rhythmic variations of nearly all physiologic parameters as reviewed by Halberg (1969),[61] to more accurately quantify the limits or parameters of "health." Rhythmic systems in mammals when challenged at various circadian stages has been shown to result in varying degrees of response as described in a review by Reinberg and Halberg (1971).[62]

Tests are not currently available to screen for an individual's hypersusceptibility to nitroglycerin.

ANALYTICAL TECHNIQUES

Nitroglycerin produces many of its pharmacologic effects at very low doses and thus small quantities are used. The metabolism of nitroglycerin is also very rapid. Thus, a combination of these two factors results in low nitroglycerin concentrations in blood plasma. Recently, Blumenthal et al. (1977)[63] have developed and published an analytical procedure with which nitroglycerin levels as low as 0.1 ng/ml can be accurately quantified in human plasma.

The ability to measure nitroglycerin in human plasma at concentrations which produce relief from coronary chest pains suggests that this method may be capable of measuring nitroglycerin levels in ammunition plant employees since the latter group also experience pharmacologic effects from their work exposures. Thus, this level of analytical sensitivity may permit quantitation of nitroglycerin levels which may produce withdrawal effects.

INDUSTRIAL HYGIENE/OCCUPATIONAL HEALTH SURVEYS

McConnell et al. (1946)[64] published a survey of occupational diseases in government-owned explosives plants manufacturing 90 to 95 percent of all explosives and ammunition produced in the United States during World War II. They showed the prevalence of occupational diseases which included a survey of workers exposed to nitroglycerin. The results of more recent studies at Army Ammunition Plants (AAP's) producing nitroglycerin are discussed below.

The data presented in this section include adverse health effects in workers at two Army Ammunition Plants producing nitroglycerin. A quantitative determination of nitroglycerin concentrations in the air at the specific locations where the presumed exposure(s) occurred are also given. The Badger Army Ammunition Plant (BAAP) at Baraboo, Wisconsin and the Radford Army Ammunition Plant (RAAP) at Radford, Virginia were two AAP's producing and processing nitroglycerin. At present only RAAP is actively involved in nitroglycerin production.

Occupational Health Survey at Badger Army Ammunition Plant

A comprehensive evaluation of nitroglycerin operations and a medical survey of workers exposed to nitroglycerin was performed at BAAP by the United States Army Environmental Hygiene Agency (1971).[65,66] At BAAP, the report states that the adverse occupational health effects discussed in the report are primarily due to nitroglycerin. Ethylene glycol dinitrate frequently added to lower the freezing point of nitroglycerin was not used at BAAP and therefore was not a contributing factor to the health problem.

A total of 136 men and 130 women worked in areas of potential nitroglycerin exposure. Of this group, 33 workers were suspected of suffering from adverse effects of nitroglycerin exposure. The adverse effects were: evidence of heart disease appearing subsequent to employment (10 workers), chest pains (6), and death (2), and headaches or rash with no other symptoms attributable to nitroglycerin (7). The remaining eight had no cardiovascular disease or any evidence of cardiac pathology at the time of employment. No diagnosis was given in the medical records as to the cause of death of either employee. In a separate random survey of 83 of the 266 employees potentially exposed to nitroglycerin at BAAP, 75 (90%) experienced headaches, and 10 showed electrocardiographic evidence of myocardial disease. The report did not indicate whether these 10 are the same individuals mentioned earlier. Many employees reported severe headaches on returning to work after an absence of a week or more and only a few reported headaches after only a weekend away from work. Thus, the tolerance to nitroglycerin-induced headaches seems to last approximately a week in workers presumably removed from nitroglycerin exposures.

Although no intensive study of occupational health problems associated with nitroglycerin was conducted at RAAP, the results of industrial hygiene surveys reveal that nearly all of the sampled areas have a nitroglycerin concentration greater than 0.02 ppm. Concentrations greater than 0.02 ppm are known to result in headaches.[67] Exposures of approximately a week and perhaps less result in the development of tolerance. If the state of tolerance to headaches is related to systemic cardiovascular changes, these workers are potential candidates for the "coronary-withdrawal-effects." The severity of the withdrawal effects at doses below the established Threshold Limit Value (TLV)[67] has not been quantitatively evaluated and thus the total health hazard of nitroglycerin exposure to workers at AAP's is yet to be established.

Industrial Hygiene Surveys at Radford and Badger Army Ammunition Plants

The results from the industrial hygiene surveys included in this report as Table 3 represents data from RAAP (1974).[68] Similar data from BAAP[66] is given in Table 4. Only data concerning nitroglycerin are presented. Included in the tables are brief descriptions of the particular operation at which each sampling was conducted, concentrations detected, and general remarks noted. In each table, "operation" describes the specific plant activity at which the sampling was conducted. The air concentrations vary at different operations but these values are not directly comparable since the sampling protocol at each operation may have differed. For example, a "general atmosphere" measurement is likely to have been taken at a greater distance from the source of nitroglycerin emissions than the samples collected "3 feet from machine." At RAAP, none of the measured air concentrations exceeded the TLV. Table 4 shows that air concentrations of nitroglycerin at BAAP did exceed the TLV. At this time RAAP is the only plant producing nitroglycerin for the Army.

NITROGLYCERIN RESEARCH PROJECTS CURRENTLY SUPPORTED BY THE US ARMY MEDICAL RESEARCH & DEVELOPMENT COMMAND

There are two nitroglycerin related research projects being supported by the US Army Medical Research & Development Command and technically monitored by the staff at USAMBRDL to study the biologic effects of nitroglycerin. The first is a contract at Midwest Research Institute (DAMD 17-74-C-4073) entitled "Munition Compounds Mammalian Toxicity Study." The second contract at Stanford Research Institute (DAMD 17-76-C-6068) is entitled "Evaluation of the Occupational Health Hazards of Trinitroglycerin Using Mammalian Models."

In a first report by Lee *et al.* (1975),[69] acute oral LD_{50}'s of nitroglycerin were determined for rats and mice of both sexes. Primary skin and eye irritation and dermal sensitivity tests were conducted as well as a study of the disposition and metabolism of nitroglycerin (NG-1,3-^{14}C).

TABLE 3. RESULTS OF ANALYSES OF ATMOSPHERIC SAMPLES FOR NITROGLYCERIN AT RADFORD ARMY AMMUNITION PLANT

Operation	Concentration,[a] ppm	mg/m^3	Remarks
NG buggy storage	0.03	0.28	General work area
Process lab	0.01	0.09	do
Mixing slurry containing nitrocellulose & nitroglycerin	0.10	0.94	do
	0.02	0.19	do
Cutting powder sheets	0.04	0.38	do
	None	--	do
Final roll of M8 powder (contains 49% NG)	0.14	1.30	Breathing zone of operator
	0.12	1.11	do
Even speed rolling of M8 powder	0.04	0.37	Sampled 3' from machine
	0.05	0.46	
do	0.02	0.19	do
	0.04	0.37	
Charging M30 propellant for 105 mm shells	0.11	1.02	General atmosphere
Pulling M30 propellant for 105 mm shells	0.05	0.46	do
Cutting M30 propellant	0.12	1.11	Breathing zone of operator
	None	--	

a. TLV = 0.2 ppm or 2 mg/m^3.

TABLE 4. RESULTS OF ANALYSES OF ATMOSPHERIC SAMPLES FOR NITROGLYCERIN AT BADGER ARMY AMMUNITION PLANT

Operation	Concentration,[a] ppm	mg/m^3	Remarks
Nitroglycerin Manufacturing Area			
Loading nitroglycerin into the prewash tank skimming of spent acid	0.15 0	1.39 0	Breathing zone
Supervision of nitroglycerin coming down trough into neutralizer tank	0.02 0	0.19 0	Breathing zone
Nitroglycerin is stored and transferred to the "angel buggies"	0.18 0	1.67 0	Breathing zone during transfer operation
Nitroglycerin transferred to "NG buggies" for Ball Powder Area	0.05 0	0.46 0	do
Rocket Propellant Manufacturing-Paste Area			
Nitroglycerin mixed with nitrocellulose in water slurry	0 0.03 0.64 0.51	0 0.28 5.94 4.73	Breathing zone General area during mixing
Centrifuging slurry	0.15 0.20 0.24 0.14	1.39 1.86 2.23 1.30	Breathing zone of wringer operator - no filter Breathing zone of wringer operator - with filter
Filling and tying bags	0.28 0.43 0.03 0 0.19 0 0.02	2.60 3.99 0.28 0 1.76 0 0.19	Breathing zone of men filling bags - no filter Breathing zone of men filling bags - with filter Breathing zone over scale - no filter Breathing zone over scale - with filter

Table 4 (continued)

Operation	Concentration,[a] ppm	mg/m^3	Remarks
	0.61	5.66	Breathing zone of tier in aisle - no filter
	0	0	do
Drying rocket propellant	0	0	
	0.71	6.59	
Screening of propellant upstairs	0.18	1.67	Breathing zone - no filter
	0.16	1.48	
	0.38	3.53	
	0.13	1.21	Breathing zone - with filter
	0	0	
	0.03	0.28	
Filling canisters with blended propellant	0.76	7.05	Breathing zone - no filter
	1.25	11.60	
	0.74	6.87	
	1.35	12.53	
	0.06	0.56	Breathing zone - with filter
	0	0	
Rocket Propellant Manufacturing-Roll and Press Area			
Preparation of propellant blankets on even and differential speed compounding rolls	0.18	1.67	Weighing for and loading differential speed bays - breathing zone
	0.04	0.37	
	0.08	0.74	
	0	0	
	0	0	Unloading differential speed bay and loading even speed bay - breathing zone
	0	0	
	0	0	Rework weighing room - general area
	0.30	2.78	
	0.11	1.02	Even speed bay - vicinity of breathing zone
	0.05	0.46	
	0.32	2.97	
	0.19	1.76	
do	0.19	1.76	do
	0.42	3.90	
do	0.30	2.78	General area of cart in dispatch bay
	0.23	2.13	
	0.12	1.11	

Table 4 (continued)

Operation	Concentration,[a] ppm	mg/m^3	Remarks
Preparation of propellant blankets on even and differential speed compounding rolls	0.17 0.38	1.58 3.53	Even speed bay - vicinity of breathing zone
do	0.24 0.32	2.23 2.97	do
do	0.30 0.15	2.78 1.39	do
Sweeping out the differential speed bay	0.25 0.24	2.32 2.23	Breathing zone
Slitting blankets	0.12 0.09	1.11 0.84	Breathing zone
Loading bay for slitter Dispatch bay	0.20 0.07 0.02 0.03	1.86 0.65 0.19 0.28	General area
Making carpet rolls	0.58 0.03	5.38 0.28	Breathing zone
do	0.72 0.15	6.68 1.39	
Extruding rocket strands	0.21	1.95	Breathing zone of press loader
	0.03	0.28	General area of press loader
	0	0	General area of carpet roll receiving box
	0.10 0 0	0.93 0 0	General area of control room
Heat treating propellant	0.14 0.65	1.30 6.03	Building had been open for 10 minutes
do	0.99 0.83	9.19 7.70	Closed building
do	0.30 0.04	2.78 0.37	Building had been open for 1 hour

Table 4 (continued)

Operation	Concentration,[a] ppm	mg/m^3	Remarks
Feeding remote doweling machine	0.06	0.56	Breathing zone
	0.06	0.56	
Inspection	0.12	1.11	Breathing zone
	0.13	1.21	
Spiral wrapping of propellant Sweco separator	0.06	0.56	General area
	0.13	1.21	
	0	0	General area
	0.6	0.56	
	0.04	0.37	
	0.04	0.37	
Inspection and sleeving	0.04	0.37	General area
Trim overlap	0.12	1.11	
	0	0	Breathing zone
	0	0	
Feeding the remote saw	0.35	3.25	Breathing zone
	0.09	0.84	
Removing grain from saw	0.01	0.09	do
Loading carts with grain	0.02	0.19	do
Grain receiving	0.01	0.09	General area
Inspection and packaging	0.05	0.46	do
	0	0	
Heating propellant	0.56	5.20	General area in 125°
	0.76	7.05	bay
Guillotining propellant	0.20	1.86	Breathing zone
	0.14	1.30	
Chipping machine	0.19	1.76	do
	0.03	0.28	
Coring operation	0.10	0.93	do
	0.71	6.59	
Drying ball powder	0.05	0.46	Breathing zone loading
	0.24	2.23	and unloading trays

a. Nitroglycerin TLV = 0.2 ppm.

A subsequent report for Phase II (1976)[54] describes the effects of subchronic toxicity studies where nitroglycerin was administered orally in food for up to 90 days in dogs, rats and mice. In addition, metabolic studies showed the pathways of nitroglycerin breakdown to be similar in rats, mice, rabbits, dogs and monkeys. Two-year chronic feeding studies in rodents are currently underway at Midwest Research Institute as well as a 6 month study in dogs to evaluate the long-term effects of nitroglycerin intake. Nitroglycerin before and after metabolic activation shall be screened for any mutagenic activity using strains of Salmonella typhimurium in the Ames assay.

In another study at Stanford Research Institute (DAMD 17-76-C-6068), telemetry units with probes attached directly on the coronary artery to measure flow rates by the doppler principle as well as probes to measure left ventricular pressure and also EKG were implanted in dogs. Measurements are taken prior to, during and after exposure of dogs to nitroglycerin. Compensatory non-oculusive coronary vasoconstriction, possibly leading to local ischemia, has been postulated to occur during the withdrawal phase. This postulate is being examined.

RECOMMENDATIONS FOR RESEARCH

1. Determine the minimum nitroglycerin dosage capable of producing tolerance with chronic administrations.

2. Determine whether compensatory constriction of the coronary vessels occur following withdrawal from long-term nitroglycerin exposures.

3. Determine the cardiovascular dose-response characteristics during withdrawal from long-term nitroglycerin exposures.

4. Determine effect of hyperthyroidism on any coronary vascular response to withdrawal from long-term nitroglycerin exposures.

5. Determine the effect of physical exertion during withdrawal from long-term nitroglycerin exposures.

6. Develop a rapid screening test based upon biochemical, physiological or other parameter(s) that is predictive of an individual's hypersusceptibility to nitroglycerin.

7. Quantitate nitroglycerin concentration in plasma samples of nitroglycerin plant workers and correlate with cardiovascular symptoms.

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